REMARKS

Please reconsider this application in view of the above amendments and the following remarks. Applicant thanks the Examiner for carefully considering this application.

Disposition of the Claims

Claims 1-71 were pending. Claim 4 has been cancelled. Therefore, claims 1-3 and 5-71 are pending after the amendments. Claims 26-52 have been withdrawn. Therefore, claims 1-3, 5-25 and 53-71 are under consideration. Claims 1, 2, 10, 14, 53, and 57 are independent. The remaining claims depend, directly or indirectly, from these independent claims.

Claim Amendments

Claims 2, 12, 24, 55 and 70 were amended by this reply to clarify the recited invention to include the diseases recited in claim 4, which is now cancelled. The amendments are fully supported by the specification as originally filed and do not constitute new matter.

Priority

The present application claims the priorities of U.S. Provisional Application Nos. 60/491,116 (filed July 30, 2003), 60/491,080 (filed July 30, 2003), 60/491,141 (filed July 30, 2003), 60/491,322 (filed July 30, 2003), and 60/491,140 (filed July 29, 2003).

The Examiner granted the priority claim only to provisional application No. 60/491,140, filed July 29, 2003. (Office Action, p. 3, first paragraph). The Examiner refused to recognize the priority claims of other provisional applications because "[t]hese provisional

applications fail to provide any support for the elected group." (Office Action, p. 2, last line – p. 3, first line).

Applicant respectfully submits that the priority claims should not be denied or canceled simply because they are not related to the "elected" subject matter due to restriction requirement. The non-elected subject matter can be filed in a divisional or continuation application. Such follow-on applications will need the priority claims.

For reasons set forth above, Applicant respectfully requests that the Examiner withdrawal the denial of the priority claims.

Claim Rejections under 35 U.S.C. § 112, ¶ 1

Claims 1-9, 12, 24, 55, and 70

Claims 1-9, 12, 24, 55, and 70 are rejected under 35 U.S.C. 112, first paragraph, as not being enabling for a person skilled in the art to practice the invention. This rejection is respectfully traversed.

Legal standard

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain*

Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985)."

Furthermore, a patent need not teach, and preferably omits, what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986); *see also*, MPEP § 2182.

The Examiner states that "the specification, while being enabling for *in vitro* inhibition of stearoyl-CoA desaturase (SCD), does not reasonably provide enablement for treatment or prevention of any disease or disorder linked to stearoyl CoA desaturase and for the simultaneous treatment and prevention of a disorder mediated by SCD." (Office Action, p. 3). Applicants respectfully submit that the Examiner has provided no evidence or data to support the statement. In fact, the cited reference Dobrzyn *et al.* (2008) contradicts the Examiner's allegation and states that "[b]ased on their *in vitro* activity, it is probable that these [SCD inhibitor] compounds could be of therapeutic value for the treatment of disorders connected with obesity."

In addition, Applicants respectfully note that testing these compounds on patients having the diseases or disorders is not a requirement for medical treatment claims using pharmaceutical compounds or compositions, nor is direct result showing treatment of the claimed diseases necessary. The proper inquiry is whether the tests/results described in the

specification, coupled with the existing knowledge in the art, would be sufficient to guide one skilled in the art to practice the invention without undue experimentation.

"An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention. . . . if the art is such that a particular model is recognized as correlating to a specific conditions, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). *See also*, USPTO Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, First Paragraph – Enablement of Chemical/Biotechnical Applications (hereinafter "USPTO Training Materials").

"The evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art." *See*, USPTO Training Materials. That the evidence provided by applicant need not be conclusive is important because the nature of scientific inquiries often does not permit the scientist to make a definite conclusion. Therefore, the proper legal standard has always been whether one skilled in the art would be convinced that a correlation exists between the data/model and the claimed methods/uses. The Examiner should not substitute personal opinion for this determination. Moreover, Applicants submit that the Examiner has not provided any actual evidence which refutes the truth or accuracy of the inventor's statement in the specification that the compounds of the invention are useful for

treating diseases mediated by SCD, including type II diabetes, obesity, dyslipidemia, metabolic syndrome, and acne in humans.

For reasons set forth below, Applicant respectfully submits that, in view of the prior art knowledge, a correlation exists between the disclosed information and the claimed methods, and one skilled in the art would not need undue experimentation to practice the invention

In view of the state of the art at the time the instant application was filed (see discussion below), one skilled in the art would reasonably expect that the compounds of the invention, would be useful in treating diseases mediated by SCD, including type II diabetes, obesity, dyslipidemia, metabolic syndrome, and acne in humans.

Type II diabetes

It is well-known that patients with type II diabetes produce insulin, but lose the ability to respond to insulin signaling, i.e., the patients have decreased insulin sensitivity. In addition, it is known that inhibition of stearoyl-CoA desaturase-1 activity can increase insulin sensitivity, thereby preventing or treating Type II diabetes.

For example, Ntambi J.M. *et al.*, *Proc. Natl. Acad. Sci.*, (August 20, 2002), Vol. 99, No. 17, pp. 11482-6, showed that mice with disrupted stearoyl-CoA desaturase-1 activity have increased insulin sensitivity (see first paragraph, pp. 11482). Moreover, it was shown (on page 11484) that stearoyl-CoA desaturase-1 knock-out mice exhibited improved glucose tolerance and a greater response to glucose lowering effect of insulin when compared to wild-

type mice. These data support the conclusion that inhibition of stearoyl-CoA desaturase-1 activity would lead to increased insulin sensitivity, which is a desired endpoint for the treatment of Type II diabetes.

Obesity

Park, E.I. *et al.*, *J. Nutr.* (1997), Vol. 127, pp. 566-573 (submitted herewith), showed that mice provided with a diet that lowered the expression of stearoyl-CoA desaturase-1 had lower body weight and lower serum concentrations of total cholesterol, triglycerides, and HDL cholesterol. Furthermore, Ntambi *et al*, cited above, demonstrated that loss of stearoyl-CoA desaturase-1 function (activity) protected mice from gaining weight from a high-fat diet.

Dyslipidemia

WO 2001/062954 disclosed an animal model for testing SCD inhibitors in lowering triglyceride, LDL and VLDL serum levels (see Example 1) and demonstrated a correlation between stearoyl-CoA desaturase-1 activity in humans and levels of serum triglycerides (see Example 2). Furthermore, as noted by Miyazaki, M. *et al.*, *Journal of Lipid Research* (2001), Vol. 42, pp. 1018-1024 (submitted herewith), triglyceride synthesis was dramatically reduced in the liver of SCD -/- mice fed a lipogenic diet compared to normal mice. See also Miyazaki, M. *et al.*, *J. Biol. Chem.* (2000), Vol. 275, No. 39, pp. 30132-30138 (submitted herewith). Furthermore, as noted in Attie, A.D. *et al.*, *Journal of Lipid Research* (2002), Vol. 43, pp. 1899-1907, SCD activity is rate-limiting in triglyceride production in a wide array of dyslipidemias. These observations demonstrated that the induction of triglyceride synthesis is highly dependent upon the expression of the stearoyl-CoA desaturase-1 gene.

Metabolic Syndrome

"Metabolic syndrome" is a recognized clinical term and has been used to describe a condition comprising at least one of type II diabetes, impaired glucose tolerance and insulin resistance, together with at least two of the following maladies hypertension, obesity, hypertriglyceridemia, low HDL or microalbuminemia. In other words, the term "metabolic syndrome" is used to describe a cluster of metabolic abnormalities. Disorders like "dyslipidemia, hypertension and obesity" are merely components of the metabolic syndrome and inhibition of stearoyl-CoA desaturase-1 activity can be a therapeutic treatment for each of these disorders individually or collectively. SCD is a key regulator of fatty acid metabolism and insulin action (*see* Ntambi, J.M. *et al.*, *Journal of Lipid Research* (1999), Vol. 40, pp. 1549-1558, submitted herewith). Therefore, a compound that inhibits SCD activity can impact more than one component of the metabolic syndrome.

Acne

Zheng *et al.*, *Nat. Genet.* (1999) 23:268-270 (submitted herewith), showed that rodents lacking a functional SCD1 gene had changes to the condition of their eyes, skin and coat thereby reducing the excessive sebum production that typically results in the formation of acne. As noted by Miyazaki *et al.*, *J. Nutr.* (2001), Vol. 131, pp 2260-68 (submitted herewith), SCD1-/- mice developed cutaneous abnormalities and atrophic sebaceous and meibomian glands compared to normal mice. These observations demonstrated that reduction of the sebum production can be effected by the inhibition of SCD1 and inhibitors of SCD are useful in treating acne in humans.

In view of the foregoing, Applicants respectfully submit that the Specification, coupled with existing knowledge in the prior art, is clearly enabling for methods of treating disease mediated by SCD, including type II diabetes, obesity, dyslipidemia, metabolic syndrome and acne. Specifically, one skilled in the art would expect the SCD inhibitors of the invention can be used to treat these SCD-mediated disorders. More importantly, it would not require undue experimentation for one skilled in the art to practice the invention.

The following will specifically address the *in re Wands* factors:

1. The nature of the invention and the breadth of claims

The Examiner states "[t]hus, the claims taken together with the specification imply that compounds of formula (I) can be used to inhibit SCD or any disease mediated by SCD." (Office Action, page 4)

Diseases mediated by SCD are not of unknown scope. As noted above, prior art is replete with evidence that inhibition of SCD can be effective in treating diseases mediated by SCD. One skilled in the art would not doubt that other diseases mediated by SCD can also be controlled by the inhibition of SCD. Applicants respectfully note that there is no need to demonstrate every single species included in a genus.

"For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art – in view of level of skill, state of the art and the information in the specification – would expect

the claimed genus could be used in that manner without undue experimentation." (*see* USPTO Training Materials).

2. ***The state of the prior art and predictability or unpredictability in the art***

Examiner cites (1) Dobrzyn *et al.* (*Expert Opinion in Therapeutic Patents*, 2008, 18(4), 457-460) as stating, "that future research is needed to determine of SCD inhibition is useful;" and (2) Boss *et al.* (*Expert Opinion in Therapeutic Targets*, 2006, 10(1), 119-134) as stating "that future research is needed to determine if SCD is a suitable target for treatment of obesity." (Office Action, page 4)

Dobrzyn *et al.* (2008)

With respect to the Examiner's comments regarding Dobrzyn *et al.* (2008), it would appear that the Examiner has taken statements made therein out of context. The Examiner specifically relied on statements in section 4 (Expert Opinion) on page 459, which states that further work is needed to validate the novel inhibitors of SCD. However, Dobrzyn *et al.* (2008) makes the above statement in connection with the patent evaluation of the specific cyclic amine SCD derivatives disclosed in the PCT Published Application WO2007/134457, which was the purpose of the article, and was not intended to be applicable to SCD inhibitors generally. Moreover, Applicants respectfully note that Dobrzyn *et al.* (2008) does not really cast doubt on the rationale of using SCD inhibitors to treat SCD-mediated diseases given the statement "[b]ased on their *in vitro* activity, it is probable that these compounds could

be therapeutic value for the treatment of disorders connected with obesity, but more experimental and clinical studies need to be done to validate these novel SCD inhibitors." (Abstract) In fact, an earlier publication from the same author showed that SCD1-deficient mice have increased energy expenditure, reduced body adiposity, increased insulin sensitivity and are resistant to diet-induced obesity and liver steatosis, and concluded that pharmacological manipulation of SCD activity can be of benefit in the treatment of obesity, diabetes, liver steatosis and other diseases of the metabolic syndrome (see Abstract; Dobrzyn, *et al.*, (2005) *Obesity Reviews*, 6:169-174 (submitted herewith).

Boss *et al.*

Applicants respectfully disagree with the Examiner's position that Boss *et al.* suggested that further research is needed to determine whether or not SCD is a suitable target for treating obesity. Instead, Boss *et al.* took the position that "SCD1 as a valuable target to treat obesity" (section 2.5). In coming to this conclusion, Boss *et al.* relied on several lines of evidence: 1) targeted disruption in SCD1 gene (*i.e.* SCD1 Knock-out) or a natural inactivating mutation in SCD1 (*i.e.* Asebia mouse) were found to be resistant to high-fat diet-induced obesity, and ii) treatment of mice with SCD1 antisense specifically repressed the expression of SCD1 in liver and adipose tissue resulted in prevention of diet-induced obesity.

Moreover, Paillard, *et al.*, 2008, *Nutr. Metab. Cardiovasc. Dis.* 18(6):436-440 (submitted herewith), have assessed the relationship between SCD activity and

triglyceridemia and abdominal adiposity in 134 men, and concluded that SCD could represent a target for prevention and treatment of these metabolic disorders in particular in subjects at risk of developing a metabolic syndrome. (Abstract).

Two recent studies in human subjects further indicate a correlation between SCD activities and diseases: (1) Sjogren, *et al.* (*Diabetologia*, (2008) 51:328-335; submitted herewith) confirmed a relationship between SCD activity and obesity/insulin resistance, previously observed in rodents, in humans. (2) Warensjo, *et al.*, *Obesity* 15:1732-1740, 2007, which showed a relationship between SCD activity (affected by SCD gene polymorphisms) and obesity/insulin sensitivity in 1143 men. (submitted herewith). These studies prove that majority of the skilled artisans are correct and that Dobrzyn's and/or Boss's doubt, if any, is unjustified.

In light of the prior art references supporting the notion of using SCD inhibitors as therapeutic agents for treating SCD-mediated diseases, the Examiner should not rely too much on Dobrzyn and Boss. *See* the USPTO Training Materials cited above ("Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition").

3. ***The amount of direction or guidance presented and the presence or absence of working examples***

As acknowledged by the Examiner, the specification enables the inhibition of SCD *in vitro*. The Examiner states, referring to page 27 (lines 3-11), "the specification does not provide guidance for alleviation or prevention of any disorder mediated by SCD." (Office Action, page 5)

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). A patent need not teach, and preferably omits, what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986); *see also*, MPEP § 2182.

The Examiner implies that the specification does not provide working examples in humans. Again, the legal standard is whether one skilled in the art would believe the animal model correlates with the treatments claimed; there is no requirement that a pharmaceutical agent must be demonstrated in human. Applicants submit that it is abundantly clear that one skilled in the art would believe the mouse model would correlate with the human diseases, and this has been demonstrated by Sjogren, *et al.*, Paillard *et al.*, and Warensjo *et al.* as noted above.

The present Specification provides a general guidance for preferred dosage range (page 46, lines 17-25) and modes of administration (page 39, lines 4-23). A person with ordinary skill in the art who will be using these therapeutic agents is probably a

researcher, a pharmacist or a physician. These people, who would be someone with an M.D. and/or Ph.D. degree in the related field, would know how to determine the optimal dosage and the optimal method of administration for treating SCD-mediated diseases in humans. Applicants respectfully submit that there is no need to include detailed information as to how to find the optimal dosages and how to administer these dosages to a patient.

4. The quantity of experimentation necessary

The Examiner states, with regard to claims 1-9, 12, 24, 55, and 70, "the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims." (Office Action, page 5)

As noted above, there is abundance of knowledge in the art in using SCD inhibitors to treat SCD-mediated disorders. Furthermore, the present Specification provides adequate guidance with a dosage range and methods of administration. Procedures for determining optimal dosage range and optimal method of administration are routine and known to a skilled artisan. The particular area of art is not speculative. Therefore, the Applicant submits that one skilled in the art would not need "undue experimentation" to use the present invention.

Claim Rejections under 35 U.S.C. § 112, ¶ 2

Claims 2, 3, 12, 24, 55, and 70

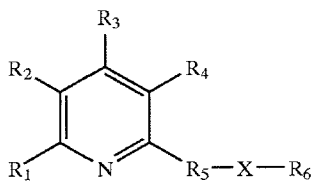
Claims 2, 3, 12, 24, 55, and 70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner stated that it is unclear what disease/disorder mediated by SCD is intended to be alleviated or prevented. In response, Applicants have amended claims 2, 12, 24, 53 and 70 to incorporate the specific SCD mediated diseases recited in claim 4. Accordingly, withdrawal of this rejection is respectfully requested.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 57, 58, 61, and 71

Claims 57, 58, 61, and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen *et al.* (U.S. Patent No. 6677452) (hereinafter "Chen"). This rejection is respectfully traversed.

Embodiments of the invention relate to compounds having a core comprising a piperazine bonded to the 3-position of a pyridine ring, as shown in independent claims 10, 14, and 53.

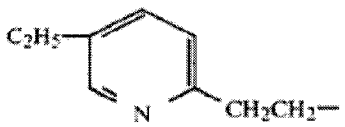


In contrast, Chen discloses pyridine carboxamide or sulfonamide derivatives having a general structure shown above, wherein one of R_1, R_2, R_3, or R_4 comprises a carboxamide or sulfonamide group (Col. 3, lines 1-2). When R_5 is piperazine, the compounds look like compounds of the invention (Example 1, columns 32 and 33). However, the piperazine is bonded to the 2-position of the pyridine ring in Chen's compounds, whereas compounds of the invention has a piperazine attached to the 3-position of the pyridine ring. Therefore, Chen's compounds are structurally distinct from compounds of the present invention.

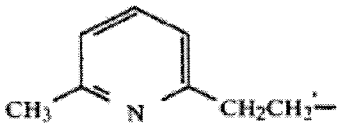
In *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.* (Fed. Cir. 2006-1329; June 28, 2007), Federal Circuit held: "[a] known compound may suggest its homolog, analog, or isomer because such compounds 'often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.' We clarified, however, that in order to find a *prima facie* case of unpatentability in such instances, a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required. Id. (citing *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992); *Dillon*, 919 F.2d 688; *Grabiak*, 769 F.2d 729; *In re Lalu*, 747 F.2d 703 (Fed. Cir. 1984))." (Emphasis added).

In the *Takeda* case, the Court held that Takeda's compound (structure shown below; left), which has an ethyl group attached to the 5-position of the pyridine ring, is not rendered obvious by a prior art compound having a methyl attached to the 6-position of the

pyridine ring (shown below; right) because the prior art does not suggest the particular modification necessary to achieve the claimed compound.



Takeda's compound



Prior art

The compounds of the present invention and the compounds in Chen are positional isomers, similar to the situations in the *Takeda* case. As in the *Takeda* case, Chen does not teach or suggest the particular modification necessary to achieve the compounds of the present invention. Therefore, Chen cannot render claims of the present invention obvious.

Furthermore, Chen discloses the compounds as a combinatorial library for screening therapeutically useful compounds (Col. 2, lines 39-42). Chen does not teach or suggest any of these compounds can be used to inhibit SCD. Therefore, even if one assumes, *arguendo*, that the compounds of the invention and compounds of Chen are simple positional isomers, compounds of the invention do have new and unexpected utilities, and, therefore, compounds of the invention would not be obvious over Chen. *In re Norris* 179 F.2d 970 (C.C.P.A. 1950).

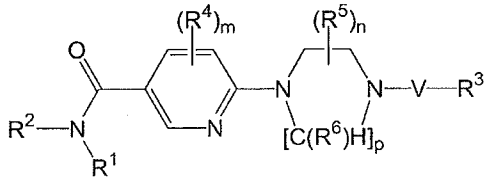
For reasons set forth above, Chen cannot render these claims obvious. As a result, claims 57, 58, 61 and 71 are patentable over Chen. Accordingly, withdrawal of this rejection is respectfully requested.

Double Patenting

Claims 2-4, 6, 10, 11, 13-16, 18, 25, 53, 54, 56, 57, and 58

Claims 2-4, 6, 10, 11, 13-16, 18, 25, 53, 54, 56, 57, and 58 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 2, 4, 46, and 52 of co-pending Application No. 10/885901 ("the '901 application"). This rejection is respectfully traversed.

The '901 application discloses compounds having the following general structure:



These compounds have the piperazine ring (or its homolog) attached to the 2-postiion on the pyridine ring. In contrast, claims of the present invention are directed to compounds having a piperazine ring attached to the 3-position on the pyridine ring.

As discussed above with reference to the *Takeda* case, these are positional isomers. Without specific teaching in the '901 application for making the specific molecular modifications necessary to achieve the claimed invention, the '901 application cannot render the claims in the present invention obvious.

Accordingly, withdrawal of this rejection is respectfully requested.

Allowable Subject Matter

Claims 17, 19-23, 59, 60, and 62-69

Applicant thanks the Examiner for indicating that claims 17, 19-23, 59, 60, and 62-69 contain allowable subject matter. For reasons set forth above, Applicant respectfully

submits that the independent claims, from which these claims depend, are allowable. Therefore, Applicant respectfully defers the re-writing of these claims in independent form.

Conclusion

Applicant believes this reply is fully responsive to all outstanding issues and places this application in condition for allowance. If this belief is incorrect, or other issues arise, the Examiner is encouraged to contact the undersigned or his associates at the telephone number listed below. Please apply any charges not covered, or any credits, to Deposit Account 50-0591, Reference 17243/002001.

Dated: June 24, 2009

Respectfully submitted,

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Attachments:

Dobrzyn, *et al.*, (2005) *Obesity Reviews*, 6:169-174.

Park, E.I. *et al.*, *J. Nutr.* (1997), Vol. 127, pp. 566-573.

Miyazaki, M. *et al.*, *Journal of Lipid Research* (2001), Vol. 42, pp. 1018-1024.

Miyazaki, M. *et al.*, *J. Biol. Chem.* (2000), Vol. 275, No. 39, pp. 30132-30138.

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Ntambi, J.M. *et al.*, *Journal of Lipid Research* (1999), Vol. 40, pp. 1549-1558.

Zheng, *et al.*, *Nat. Genet.* (1999), 23:268-270.

Paillard, et al., *Nutr. Metab. Cardiovasc. Dis.*, (2008), 18(6):436-440.

Sjogren, *et al.*, *Diabetologia*, (2008) 51:328-335.

Warensjo, *et al.*, *Obesity* (2007), 15:1732-1740.